Remarks

Claims 1-5, 10, 12-16, 18-22 and 29-85 are pending. Claims 1 and 66-71 have been amended, without prejudice or disclaimer of any previously claimed subject matter. Claims 72-85 are new. Applicants reserve the right to present any withdrawn or cancelled subject matter in one or more continuation or divisional applications.

In the final Office action, dated August 19, 2004, the Examiner did not note the status of claim 4. In the previous Office action, dated December 2, 2004, the Examiner noted that claim 4 appears to be free of the art and claims 10, 12-16, 21, 22 and 66-71, amended to depend from claim 4, would also appear to be free of the art. New claims 72-85 depend from claim 1 or 4 (directly or indirectly) and thus are submitted to be allowable.

The Examiner has rejected pending claims 1, 3, 5, 10, 12-16, 18-22 and 29-71 under 35 U.S.C. § 112, first paragraph. This rejection is traversed to the extent that it applies to the amended claims.

The specification provides detailed description which supports the claims as amended. In particular, the present application is directed to sphingolipid prodrugs and uses thereof. It has been discovered that biologically important sphingolipids can be administered as prodrugs which increase the level of active compound that is delivered to the active site of interest.

As discussed on page 67 of the application, one problem associated with the administration of sphingolipids as therapeutic agents is that they can be metabolized before they reach the target location. This can be a particular problem if the target location is distant from the site of administration. For example, perhaps only 5-10% of a sphingolipid reaches the lower

intestine in the delivered form. Since sphingolipids of milk origin have been determined to have a therapeutic effect on intestinal tumors, the low bioavailability to that region is troublesome.

This problem has been addressed by providing a sphingolipid, or an analog or physiological derivative thereof, alone or in combination, as a prodrug that includes an R^2 substituent, including those of Formula I, that is cleaved by an appropriate enzyme *in vivo* to release a parent sphingolipid moiety for desired therapy. Certain derivatives of Formula I are especially suited for treatment of disorders of the lower intestinal tract, including but not limited to colon cancer, intestinal polyps, intestinal tumors, inflammatory bowel diseases including ulcerative colitis and Crohn's disease, necrotizing enterocolitis, ileocecitis, other inflammations of the lower bowel, and antibiotic associated colitis, as the enzymes which free the sphingolipid from its prodrug form are concentrated in the lower intestine. These prodrugs are resistant to hydrolysis in the upper gastrointestinal tract, and are more readily cleaved in the cecum and the colon. It is not necessary that the compound undergo no metabolism in the upper GI tract, rather, it is preferred that a sufficient portion survive and be cleaved in the colon.

For example, the b-D-galactoside derivatives of Formula I can be cleaved by b-D-galactosidase. N-acetyl-b-D-glucosamine derivatives can be acted on by N-acetyl-b-D-glucosaminidase. The a-D-mannoside derivatives of Formula I are substrates for a-D-mannosidase. The b-D-cellobiosides, b-D-glucopyranosides, b-D-galactopyranosides, and b-D-glucuronides are substrates for glycosylhydrolases. Multiple enzymes from colonic bacteria are able to digest starch (such as maize starch, amylo-maize starch, pectin and others found in wheat flour, potato and beans). Multiple enzymes of colonic bacteria are also capable of cleaving lactose, raffinose, stachyose, and fructooligosaccharide (such as oligofructose and insulin) derivatives of Formula I. Compounds of Formula I which are amides and esters of b-

cyclodextrin or dextrans linked via succinate and glutarate are substrates for amidases and esterases.

The active compound which is a substrate for the colonic enzyme can be administered by any suitable means, including orally. In one embodiment, the active compound is administered in a way that promotes the intestinal microflora that produce the enzymes that cleave these pro-drugs.

The specification provides detailed support of the claimed methods. The specification provides detailed description of the prodrugs which can be used. The application discloses on pages 77-83 methods of treatment of abnormal proliferation that can be used. The specification provides on page 113-114 examples of biological activity of an exemplary prodrug. The specification provides sufficient disclosure for one of ordinary skill in the art to practice the claimed methods.

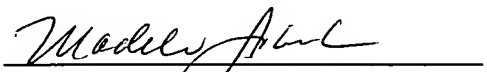
Applicants again note that the U.S. Patent Office has previously granted U.S. Patent No. 6,610,835, of which the present application is a continuation, with claims to compounds including those in the method described in claim 1. The Examiner in both cases issued restriction requirements between the compounds and the method of using the compound to treat abnormal cell proliferation. By issuing the parent case, the Patent Office has already found that the application is enabled for the compounds recited in the pending method claims.

In view of the detailed description in the specification and the amendments and arguments herein, withdrawal of the outstanding rejection is respectfully requested.

Applicants enclose a check for $905 for the Petition for Extension of Time and Request for Continued Examination fees, however, the Commissioner for Patents is authorized to charge

any additional fees which may be required, or credit any overpayment, to Deposit Account No. 11-0980.

Respectfully submitted,



Madeline I. Johnston, Esq.
Reg. No. 36,174

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King & Spalding LLP
191 Peachtree Street
Atlanta, Georgia 30303
404-572-4720 (telephone)
404-572-5145 (facsimile)